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26. Dopaminergic agents with different mechanisms of action differentially affect responding for conditioned reward

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Introduction

Primary rewarding or reinforcing stimuli such as food or water can exert powerful control over the behaviour of animals. Rewarding stimuli can alter the ability of reward-related stimuli to elicit approach or other responses in the future, a phenomenon that has been termed incentive motivational learning or, more simply, incentive learning (Bolles, 1972; Bindra, 1974; Beninger, 1983). Additionally, stimuli that become conditioned incentive motivational stimuli by this process themselves acquire the ability to act as rewarding stimuli. These conditioned rewards, like primary rewards, can alter the ability of stimuli associated with their presentation to elicit approach and other responses in the future.

The effects of conditioned rewards or conditioned reinforcers on behaviour have been evaluated with the use of a number of procedures. Mackintosh (1974) has classified these as the maintenance of responding in extinction, the establishment of a new response, and responding on second order schedules.

The first procedure is typified by a study of Bugelski (1938) who trained rats to respond for food that was signalled by the click of the feeder apparatus. He then tested the animals in extinction (food was no longer presented) and found that animals receiving the click contingent upon responding emitted more responses. He concluded that the click had become a conditioned reward. Subsequent studies showed that the performance of an established response in extinction with and without conditioned reward may be affected by generalization decrement (see Mackintosh, 1974). A better procedure was to evaluate the ability of the reward-related stimulus to control a new response. In one of the earliest studies using this procedure, Skinner (1938) presented rats with pairings of a feeder click and food and then trained the rats to press the lever for the feeder click alone. Acquisition of the response revealed the conditioned rewarding properties of the click.

One problem with the established and new response procedures is that the

animals were tested in extinction; the control of responding by conditioned rewards was gradually being lost with repeated presentations of the conditioned reward in the absence of the primary reward. Second order schedules avoid this problem (see Kelleher, 1966). Animals are trained, for example, to complete five fixed interval (FI) 1-min schedules to receive primary reward or reinforcement; this would be termed a second order fixed ratio 5 (FI 1-min) schedule. The completion of each FI is signalled with the presentation of a stimulus that has been paired with primary reward. If that stimulus is shown to control responding, for example by producing the classic FI scallop, better than a stimulus that has not been paired with primary reward, it can be said to be acting as a conditioned reward. Numerous studies have shown that reward-related stimuli presented according to second order schedules act as conditioned rewards (Kelleher, 1966).

Responding that is under the control of a conditioned rewarding stimulus has been found to be reliably affected by pharmacological agents that influence dopaminergic neurotransmission. Furthermore, the effects of these agents have been found to be related to their mechanism of action in the brain and have been localized to specific regions of the brain. The relevant studies will be reviewed in the present paper. Results suggest that assessment of the effects of pharmacological agents on responding for conditioned reward may be a useful strategy for studying compounds that may be active at dopaminergic synapses in the central nervous system.

Dopaminergic Agents Administered Systemically

Pipradrol

The earliest studies of the effects of drugs on responding for conditioned reward used the amphetamine-like stimulant pipradol. Biochemical studies have shown that pipradrol is a potent releaser of dopamine (DA) (Scheel-Kruger, 1971). Employing the established response procedure, Hill (1970) found that pipradrol enhanced responding for conditioned reward but reduced responding in extinction when no conditioned reward was presented. Robbins (1975) replicated this result with pipradol, showed that the effect was dose-dependent, and showed further that animals would choose, from among two levers, the lever that produced the conditioned reward. Numerous subsequent studies employed food, water or brain stimulation as the primary reward followed by testing for conditioned reward using the new response procedure and found that pipradrol enhanced responding for conditioned reward (Robbins, 1976, 1978; Robbins and Koob, 1978; Beninger *et al.*, 1980, 1981; Robbins and Everitt, 1982; Robbins *et al.*, 1983; Chu and Kelley, 1992).

A number of control procedures were used in these studies to ensure that pipradrol was enhancing responding for conditioned reward and not simply producing a stimulant effect. These included the finding, mentioned above, that animals discriminated between two levers to choose the lever producing condi-

tioned reward and that pipradrol produced a selective or relatively greater increase in responding on the lever (Robbins, 1975, 1976; Robbins and Koob, 1978; Beninger *et al.*, 1980,81; Robbins and Everitt, 1982; Robbins *et al.*, 1983). Hill (1970) showed that pipradrol decreased responding on a lever that produced a stimulus not previously associated with primary reward showing that the drug did not simply increase responding for stimulus change. Others (Robbins, 1978; Beninger *et al.*, 1980) found the same effect. Similarly, Robbins (1976) showed that pipradrol failed to increase responding for a stimulus randomly associated with primary reward. In an interesting study, Robbins (1976) required animals to complete a two-response chain (press lever 1 and then lever 2) to receive conditioned reward; he found that animals treated with pipradrol pressed significantly more on lever 2 reducing the number of conditioned rewards they would have received if only a single response was required. Robbins concluded that pipradrol increased the repetition of responses but that response selection was governed, at least in part, by conditioned rewards. The possibility that pipradrol increased the primary motivation for food was ruled out by Hill's (1970) finding that animals treated with the drug consumed less sweetened condensed milk.

Some studies have examined the contribution of central dopaminergic neurotransmission to the effects of pipradrol. Robbins and Everitt (1982) injected the catecholamine-selective neurotoxin 6-hydroxydopamine (6-OHDA) into either the head of the caudate nucleus or the nucleus accumbens, both terminal regions of mesencephalic dopaminergic neurons. DA depletions in the respective target areas were greater than 80%. They found that the effects of pipradrol on responding for conditioned reward were significantly reduced in both cases. Recently, Chu and Kelley (1992) examined the effects of intra-accumbens injections of the DA D_2 receptor antagonist haloperidol; the effects of pipradrol on responding for conditioned reward were significantly reduced. These results provide some evidence that dopaminergic projections to the caudate-putamen and to the nucleus accumbens may participate in the effects of pipradrol on responding for conditioned reward.

Amphetamine

Amphetamine increases the neurogenic release and blocks the uptake of DA (Scheel-Kruger, 1971; Westerink, 1979). The first two reports examining the effects of amphetamine on responding for conditioned reward using extinction procedures found no significant effect (Robbins, 1978; Beninger *et al.*, 1981). Subsequently, however, amphetamine was found to increase new responding in extinction for conditioned reward in a dose-dependent manner (Robbins *et al.*, 1983; Mazurski and Beninger, 1986; Beninger and Ranaldi, 1992). It is noteworthy that the amphetamine effect was usually not as large as that seen with pipradrol. It is possible that the earlier studies that failed to show an effect of amphetamine used procedures that produced relatively modest conditioned reward effects in control animals; as procedures were improved, producing more robust effects in non-

drugged animals, an enhancement of responding for conditioned reward by amphetamine was seen.

Recent studies have examined the effects of amphetamine on key peck responding of pigeons reward according to a second order schedule. Cohen and Branch (1991) trained pigeons on a random ratio 2 (variable interval 30-sec), i.e. RR 2 (VI 30-sec), second order schedule with sessions consisting of two signalled phases (each phase lasting approximately 30 min) and with three conditions. In the paired condition, in the first phase, conditioned reward and primary reward were presented according to the RR2 schedule and conditioned reward according to the VI 30-sec schedule. In the second phase, no primary reward was presented but conditioned reward continued to be presented according to the VI 30-sec schedule. Pigeons receiving amphetamine prior to sessions in the paired condition responded less in the first component but more in the second component. This effect was not seen in the unpaired condition, where the stimulus presented at the end of the VI 30-sec was not paired with food. Nor was this effect seen in the no stimulus condition, where no stimulus signalled the end of the VI 30-sec component. Thus, amphetamine enhanced responding for conditioned reward.

In a related study, Cohen (1991) trained pigeons on a multiple second order schedule. In this case, the component schedule was a fixed interval and primary reward was presented according to a variable interval schedule. Unlike the study of Cohen and Branch (1991), amphetamine increased responding in both the paired and unpaired condition. Perhaps the type of second order schedule influences the results that will be seen with amphetamine. However, too few data are currently available to provide an explanation for the existing results of tests of amphetamine effects on responding for conditioned rewards presented according to second order schedules.

Apomorphine

Like pipradrol and amphetamine, apomorphine is an agent that enhances dopaminergic neurotransmission but through a different mechanism. Apomorphine is a direct-acting DA agonist, mimicking the action of DA at DA receptor sites (Colpaert *et al.*, 1976). In studies using the new response procedure with two levers, one of which produced conditioned reward, apomorphine was reported to produce an indiscriminant increase in responding on both levers leading to a loss of any evidence of conditioned reward (Robbins *et al.*, 1983; Beninger and Ranaldi, 1992). Mazurski and Beninger (1986) reported that apomorphine was without significant effect on responding for conditioned reward but the dose range (0.5-1.0 mg/kg) was narrower than that used by the two studies reporting increases in responding. One study evaluated the effects of a low dose of apomorphine (0.1 mg/kg) in animals that had undergone 6-OHDA lesions of the nucleus accumbens; Taylor and Robbins (1986) found that apomorphine enhanced responding for conditioned reward in those animals with supersensitive accumbens DA

receptors. Results suggest that in normosensitive animals apomorphine produces a motor stimulant effect but the control of responding by conditioned rewarding stimuli is lost. This stands in strong contrast to the conditioned reward enhancing effects of indirect-acting DA agonists such as pipradrol and amphetamine.

DA receptor subtype-specific agonists

With the use of molecular biological studies, a number of DA receptor subtypes have been identified recently but they continue to be codified in terms of the original dichotomy of D_1 and D_2 receptors, being associated with the stimulation and inhibition of adenylate cyclase, respectively (Niznik and van Tol, 1992). A relatively selective D_1 agonist is SKF 38393 (Setler *et al.*, 1978) and bromocriptine (Markstein, 1981) and quinpirole (Tsuruta *et al.*, 1981) are selective D_2 agonists.

Recently, we have investigated the effects of these agonists with relative specificity for the D_1 or D_2 receptor family on responding for conditioned reward (Beninger and Ranaldi, 1992). Results revealed that the D_2 agonists enhanced responding for conditioned reward whereas the D_1 agonist led to a loss of control of responding by conditioned reward (Beninger and Ranaldi, 1992). The results with bromocriptine and quinpirole were surprising since apomorphine, a DA agonist that mimics the action of DA at D_1 and D_2 receptors, led to a loss of control of responding by the conditioned reward (see above). Results suggested that the disruptive effects of apomorphine on responding for conditioned reward were mediated by its action at the D_1 receptor.

DA antagonists

Some studies have evaluated the effects of DA receptor blocking drugs on the acquisition of rewarding properties by neutral stimuli paired with primary reward. Beninger and Phillips (1980) and Hoffman and Beninger (1985) treated animals with the D_2 DA receptor blocker pimozide (Pinder *et al.*, 1976; Seeman, 1981) during the pairing of a tone or lights-off stimulus with food. When the animals subsequently were tested for the learning of a new lever press response in a two lever situation with the tone or lights-off stimulus as the putative conditioned reward for pressing one of the levers, a dose-dependent impairment was seen. It is noteworthy that the animals were treated with the drug during the pairing phase but tested drug free. Apparently, pimozide had blocked the acquisition of rewarding properties by the stimulus associated with food.

Others have evaluated the effects of DA receptor blockade during the lever press acquisition phase of a conditioned reward experiment using the new response procedure. Robbins *et al.* (1983) found that the D_1 and D_2 DA receptor antagonist *cis*-flupenthixol (Nielsen *et al.*, 1973) dose-dependently blocked the acquisition of responding for conditioned reward. This finding was consistent with the results of some of the control groups of Beninger and Phillips (1980) which failed to acquire

responding for conditioned reward when treated with pimozide. These results provide evidence that intact dopaminergic neurotransmission is necessary for both the acquisition by neutral stimuli of rewarding properties during their pairings with primary reward and for the ability of established conditioned rewards to produce the learning of a new response.

Other drugs

Methylphenidate, like pipradrol, is a potent stimulator of DA release (Scheel-Kruger, 1971). It has been found to increase responding for conditioned reward in a number of studies. Robbins (1978) found that methylphenidate produced a relatively greater increase in responding on a lever that produced conditioned reward than on a second lever that produced no conditioned reward. Using pigeons responding according to a second order schedule, Files *et al.* (1989) similarly found that methylphenidate increased responding for conditioned reward. Interestingly, in that study no effect of a conditioned reward versus a signal unassociated with reward was seen in the no drug condition. Thus, methylphenidate revealed the conditioned rewarding effectiveness of the stimulus (cf. Cohen and Branch, 1991).

Perhaps surprisingly, the DA releasing drugs nomifensine (Braestrup and Scheel-Kruger, 1976) and cocaine (Moore *et al.*, 1977) failed to enhance responding for conditioned reward (Robbins, 1978; Beninger *et al.*, 1981; Robbins *et al.*, 1983). On the other hand, two cocaine analogues, WIN 35,428 and WIN 35,065-2 were found to enhance responding for conditioned reward (Robbins *et al.*, 1983). Other drugs that have failed to produce enhanced responding for conditioned reward or have decreased responding include the benzodiazepine chlordiazepoxide (Robbins *et al.*, 1983) and the opiate morphine (Robbins *et al.*, 1983), respectively.

Dopaminergic Agents Administered Centrally

DA

The DA terminal region, the nucleus accumbens, has been found to be very sensitive to the enhancing effects of many dopaminergic agents on responding for conditioned reward. Cador *et al.* (1991) microinjected DA bilaterally into the nucleus accumbens of rats prior to testing them for the acquisition of a new response rewarded with a stimulus previously paired with water. They observed a small dose-dependent enhancement with intermediate doses being most effective. Control studies that showed dose-dependent enhancement failed to occur in animals that had received random presentations of the stimulus and water during the pairing phase. The enhancing effect of DA was not seen in animals pretreated with *cis*-flupenthixol. Nor was an enhancement seen if DA was microinjected into the middle posterior region of the caudate-putamen. Finally, depletions of noradrenaline in the nucleus accumbens, effected with 6-OHDA lesions of the

dorsal noradrenergic bundle, failed to affect the enhancement produced by DA in the nucleus accumbens. These results provide strong evidence that DA in the nucleus accumbens plays an important role in the control of responding by conditioned rewarding stimuli.

Pipradrol

Chu and Kelley (1992) found that pipradrol micoinjected into the nucleus accumbens, like systemic injections, enhanced responding for conditioned reward. Accumbens pipradrol failed to affect responding significantly on a lever that did not produce a conditioned rewarding stimulus. Chu and Kelley (1992) evaluated the effects of the DA D_1 receptor antagonist SCH 23390 (Iorio *et al.*, 1983) or the D_2 antagonist raclopride (Kohler *et al.*, 1985) given systemically on the enhancement of responding produced by pipradrol injected into the nucleus accumbens. Both drugs decreased responding suggesting that stimulation of both D_1 and D_2 receptors may be necessary for the pipradrol-produced enhancement of responding for conditioned reward to occur.

Amphetamine

Many studies have shown that intra-accumbens injections of amphetamine produced a large dose-dependent enhancement of responding for conditioned reward (Taylor and Robbins, 1984, 1986; Jones *et al.*, 1990; Cador *et al.*, 1991; Kelley and Delfs, 1991*a,b*; Chu and Kelley, 1992; Cunningham and Kelley, 1992*a,b*). These injections failed to affect responding on a lever that did not produce conditioned reward (Taylor and Robbins, 1984, 1986; Jones *et al.*, 1990; Cador *et al.*, 1991; Kelley and Delfs, 1991*a,b*; Chu and Kelley, 1992) nor did they enhance responding for a stimulus that was randomly or negatively paired with primary reward (Taylor and Robbins, 1984), showing that the effects of amphetamine were specific to responding for a stimulus previously paired with primary reward.

Taylor and Robbins (1986) antagonized the effects of intra-accumbens amphetamine with 6-OHDA lesions of the accumbens but, interestingly, the conditioned reward effect still was seen. 6-OHDA lesions of the posterior region of the caudate-putamen failed to affect accumbens amphetamine-produced enhancement of responding for conditioned reward (Taylor and Robbins, 1986). This result may be seen to be at odds with the report of Robbins and Everitt (1982) that 6-OHDA lesions of the posterior caudate-putamen decreased the response-enhancing effects of systemic pipradrol. Chu and Kelley (1992) reported that the amphetamine effect was antagonized by systemic injections of SCH 23390 or raclopride showing that stimulation of both D_1 and D_2 receptors may be necessary for the effect to occur. Cador *et al.* (1991) implicated the basolateral amygdala; bilateral excitotoxic lesions of this structure significantly reduced the enhancement of responding for conditioned reward produced by amphetamine.

The effects of amphetamine in a number of brain regions besides the nucleus accumbens have been evaluated. Positive sites have been identified in the anterodorsal and middle ventrolateral (Kelley and Delfs, 1991*b*) and posterior caudate-putamen (Taylor and Robbins, 1984). Negative sites in the caudate-putamen include the anterior ventrolateral, ventromedial and posterodorsal regions (Taylor and Robbins, 1984). Other negative sites include the dorsal medial thalamus (Taylor and Robbins, 1984). As the study showing positive sites in the posterior caudate-putamen used relatively large injection volumes (2 μl), it is possible that effects were due to spread to other sites such as the nucleus accumbens; this speculation is supported by the finding that 6-OHDA lesions of this region failed to affect the enhancement of responding produced by amphetamine in the accumbens (Taylor and Robbins, 1986).

DA receptor subtype-specific agonists

Chu and Kelley (1992) evaluated the effects of intra-accumbens injections of the D_1 agonist CY 208-243 (Murray and Waddington, 1990) or the D_2 agonist quinpirole on responding for conditioned reward. Neither compound produced an enhancement. However, injection of the two in combination enhanced responding for conditioned reward suggesting a synergistic action of stimulation of D_1 and D_2 receptors. These results are in conflict with a recent report of Everitt and Robbins (1992). They found that either SKF 38393 or quinpirole alone, when injected into the accumbens, enhanced responding for conditioned reward.

Other drugs

In one study, noradrenaline was microinjected into the nucleus accumbens prior to testing the acquisition of responding with conditioned reward; no effect was seen (Cador *et al.*, 1991). Chu and Kelley (1992) found that cocaine microinjected into the nucleus accumbens, contrary to its lack of effect when administered systemically (see above), dose-dependently enhanced responding for conditioned reward. In a control study, injections of cocaine into the accumbens failed to affect responding on a lever that did not produce conditioned reward. This showed that the effects of cocaine were specific to responding for a conditioned reward.

Kelley and Delfs (1991*a*) investigated the possibility that peptides injected into the origin of the dopaminergic projections to the nucleus accumbens, the ventral tegmental area, would influence responding for conditioned reward. They injected agents known to enhance the activity of dopaminergic neurons; these included neurotensin, d-ala-met-enkephalin (DALA), morphine and substance P. In no case did injections of these agents into the ventral tegmental area alter responding for conditioned reward; substance P was observed to increase responding on both the lever that produced conditioned reward and the other lever.

Cunningham and Kelley (1992*b*) found that opioid peptides injected directly into the nucleus accumbens also failed to affect responding for conditioned reward. Thus, no effect of morphine, DALA, [D-Ala^2-N-Me-Phe^4-Gly-ol^5]-enkephalin (DAMGO) or [d-Phen^{2,5}]-enkephalin (DPEN) was seen. However, when four intra-accumbens treatments with the μ opioid receptor agonists morphine or DAMGO, one a day for four days, were followed by intra-accumbens injections of amphetamine, an enhancement of the effects of amphetamine was seen (Cunningham and Kelley, 1992*a*). The effect was not seen following a similar pre-treatment regimen with DPEN, a δ agonist. These results suggest that opiates acting at the μ receptor mediate cross-sensitization with amphetamine.

Summary

Systemic administration of indirect-acting dopaminergic agonists such as amphetamine, pipradrol and methylphenidate enhanced responding for conditioned reward in a dose-dependent manner. Control procedures ruled out the possibility that effects can be attributed to changes in motor activity or motivation for primary rewards. Perhaps surprisingly, the DA uptake blocker cocaine was seen not to increase responding for conditioned reward. In contrast to the effects of amphetamine-like drugs, the direct-acting DA agonist apomorphine failed to enhance responding specifically on the lever producing conditioned reward. When receptor subtype-specific agonists were tested, a D_1 agonist, like apomorphine, led to a loss of control of responding for conditioned reward; D_2 agonists, on the other hand, produced amphetamine-like effects, producing greater enhancement of responding on the lever producing conditioned reward. These results suggest that the disruption of responding for conditioned reward produced by apomorphine may be attributed to the action of the drug at the D_1 receptor.

Studies investigating the effects of dopaminergic agents administered directly to the brain on responding for conditioned reward have focused on the nucleus accumbens. Intra-accumbens injections of DA itself, amphetamine, pipradrol or cocaine were found to enhance responding for conditioned reward. Sites in the dorsal thalamus were inactive as were many areas of the caudate-putamen; however, amphetamine injections into the anterodorsal, middle ventrolateral and posterior caudate-putamen were seen to enhance responding for conditioned reward. Furthermore, 6-OHDA lesions of the nucleus accumbens eliminated the enhancement of responding producing by amphetamine in the nucleus accumbens but did not antagonize the conditioned reward effect itself. This result suggests that DA in brain regions other than the accumbens is involved in the control of responding by conditioned rewards. One region that was shown to participate is the basolateral amygdala; lesions there decreased the effects of accumbens amphetamine on responding for conditioned reward.

Conflicting data have been published concerning the effects of intra-accumbens injections of D_1 and D_2 receptor-specific agonists on responding for conditioned

reward. Agents relatively selective for either receptor have been reported to enhance responding and to have no effect. However, the study reporting negative results found that co-administration of a D_1 and D_2 agonist into the nucleus accumbens had a synergistic effect, enhancing responding for conditioned reward.

Reward-Related Learning may be Mediated through a DA Signal at D_1 Receptors

Reward-related learning is seen when an animal shows increased responding for stimuli that have an association with reward. Sensory stimuli, which previously did not elicit responses, acquire this ability after being paired with reward. This suggests that primary reward modifies the relationship between sensory stimuli and motor patterns. It has been suggested that this modification occurs through the action of a DA signal at D_1 receptors (Beninger, 1983; Miller *et al.*, 1990; Beninger, 1991; Benninger and Ranaldi, 1992).

The striatum, which includes the caudate, putamen, nucleus accumbens and olfactory tubercle, is the target of massive numbers of cortical glutamate-secreting afferents. The striatum also is innervated by dopaminergic neurons originating from the mesencephalon (Nauta and Domesick, 1984; Zahm and Brog, 1992). The output cells of the striatum appear to play a strong role in the control of motor activity. Hence, the striatum is a potential site for modifications of sensory-motor synapses between neurons representing various stimuli and neurons controlling responses. When an animal is presented with a primary reward at least two important neural events may occur. First, synaptic connections in the striatum between cortical afferents carrying sensory information and output motor-related cells may become active. Second, DA may be released diffusely throughout the striatum. DA, acting on those synapses that were active recently (those activated by sensory stimuli in close temporal proximity to the primary reward), may lead to a long-term strengthening of those synapses. Synaptic facilitation would constitute the acquisition by neutral stimuli of the ability to activate striatal outputs previously activated only by primary reward. Hence, neutral stimuli would come to act as conditioned rewards (Beninger, 1991).

DA may enable the putative long-term strengthening of striatal synapses through a chain of intracellular molecular events commencing with stimulation of the D_1 receptor. It has been shown that stimulation of D_1, but not D_2 receptors, led to increased cyclic-AMP formation (see Kebabian and Calne, 1979). It is believed that cyclic-AMP dependent protein kinases bring about the phosphorylation of other proteins that may modify the effectiveness of synapses. This modification may occur only in recently activated synapses that may be discriminated by increased levels of postsynaptic calcium (see Wickens, 1990).

Data from experiments examining the effects of DA afferents on responding for conditioned reward and from related studies can be seen to support the hypothesis that reward-related learning occurs through a DA signal at D_1 receptors in striatal regions. When animals are given the opportunity to consume rewards such as food

or rewarding drugs, an increase in the amount of DA released in striatal regions such as the caudate-putamen and nucleus accumbens occurs (Blackburn *et al.*, 1986; Hernandez and Hoebel, 1988; Radhakishun *et al.*, 1988; Nakahara *et al.*, 1989; Phillips *et al.*, 1991). Animals that are given access to stimuli that have a history of being paired with reward, in the absence of the primary reward, also show increased DA release (Blackburn and Phillips, 1989). These data demonstrate that stimuli that possess primary or conditioned rewarding properties can produce distinct DA signals in the brain.

One mechanism that has been proposed to explain how neutral stimuli may acquire conditioned rewarding properties is through the release of DA (Beninger, 1983; Beninger *et al.*, 1989; Miller *et al.*, 1990; Beninger, 1991, 1992; Beninger and Ranaldi, 1992). This hypothesis leads to the suggestion that amphetamine-like drugs would enhance responding for conditioned reward by enhancing the ability of reward-related stimuli to acquire the control of responding. This idea has also been expressed by other authors. For instance, Hill proposed that "... the effects of amphetamine-like drugs can be generalized as an exaggeration of the control on behaviour exerted by related environmental events" (Hill, 1970, p. 781). Likewise, Hill cites Stein's suggestion that amphetamine-like drugs produce "...a sensitization of the neural systems that mediate the processing of rewards. According to that proposal, when stimuli with established reinforcing properties impinge upon the sensitized brain 'reward' system, the effectiveness of the stimuli in controlling behaviour is increased" (Hill, 1970, p. 782).

If the release of DA serves as a signal for a rewarding event, then drugs that interfere with this signal, in contrast to amphetamine-like drugs, would impair the ability of conditioned stimuli to acquire rewarding properties and to maintain responding. This is supported by several studies showing differential effects on responding for conditioned reward by direct and indirect DA agonists. Thus, amphetamine, an indirect DA agonist (Scheel-Kruger, 1971; Westernik, 1979), enhanced responding for conditioned reward (Robbins *et al.*, 1983; Mazurski and Beninger, 1986; Beninger and Ranaldi, 1992). The similarly-acting drugs, methylphenidate and pipradrol, produced comparable effects (Hill, 1970; Robbins, 1975, 1976, 1978; Robbins and Koob, 1978; Beninger *et al.*, 1980, 1981; Robbins and Everitt, 1982; Robbins *et al.*, 1983; Files *et al.*, 1989; Cohen and Branch, 1991; Chu and Kelley, 1992). On the other hand, apomorphine, a direct DA agonist, increased responding on both levers and impaired the ability of the conditioned stimulus to control responding (Robbins *et al.*, 1983; Mazurski and Beninger, 1986; Beninger and Ranaldi, 1992). These results would be expected if responding for conditioned reward depended on an intact DA signal. Amphetamine and related drugs may have increased the putative DA signal associated with reward. Apomorphine may have masked the signal by stimulating postsynaptic DA receptors. Similar hypotheses have been used previously to explain differential behavioural effects of direct versus indirect DA agonists (Herberg *et al.*, 1976; Robbins and Everitt, 1982; Robbins *et al.*, 1983; Beninger, 1983; Beninger *et al.*, 1989; Beninger and Ranaldi,

1992). These studies support the hypothesis that an intact DA signal may be required for the acquisition of rewarding properties by conditioned stimuli.

That the putative reward signal occurs at D_1 receptors is suggested by experiments performed in our laboratory using D_1 and D_2 receptor-specific agents (Beninger and Ranaldi, 1992). Thus, when bromocriptine and quinpirole, both D_2 selective compounds, were given to animals responding for conditioned reward, they produced effects similar to amphetamine. They increased responding specifically on the lever producing the conditioned reward suggesting that these drugs enhanced the conditioned reward effect. Yet SKF 38393, a D_1 selective agonist, resulted in no effect at low doses and an impairment of responding for conditioned reward at higher doses. This might suggest that the putative masking of the reward signal produced by apomorphine takes place at the D_1 receptor.

We designed an experiment to investigate more directly the role of DA receptor subtypes in responding for conditioned reward (Ranaldi and Beninger, 1993), which challenged the amphetamine-produced enhancement of responding for conditioned reward with either D_1- or D_2-selective antagonists. It was found that SCH 23390 shifted the amphetamine dose-response function toward the right without affecting maximal responding, suggesting a direct antagonism of the conditioned reward effect. However, pimozide and metoclopramide, both D_2 antagonists, produced contradictory results. Pimozide shifted the amphetamine dose-response function to the right, similar to but to a lesser degree than SCH 23390. It also tended to lower maximal responding. Metoclopramide did not produce a rightward shift but lowered maximal responding. These findings suggest that an intact DA signal at D_1 receptors is necessary in responding for conditioned reward, that D_2 receptor stimulation plays a role in conditioned reward although this role may be different from that of the D_1 receptor. The D_2 receptor may be more involved in producing the energizing component of reward (Miller *et al.*, 1990).

Some experiments using the conditioned reward paradigm produced results that may appear to contradict the D_1 signal hypothesis. Thus, SKF 38393 (Everitt and Robbins, 1992) and DA (Cador *et al.*, 1991) enhanced responding for conditioned reward when injected directly into the nucleus accumbens of rats. Similarly, a low dose of apomorphine enhanced responding for conditioned reward in animals having undergone DA denervation of the nucleus accumbens (Taylor and Robbins, 1986). These data demonstrate that direct stimulation of accumbens D_1 receptors fails to mask the putative DA reward signal. However, there are some contradictory findings. Enhanced responding for conditioned reward was not observed when CY 208-243, another D_1-selective agonist, was injected directly into the nucleus accumbens (Chu and Kelley, 1992). In another study, injections of morphine into the ventral tegmental area, which increase DA cell firing (Ostrowski *et al.*, 1982) and synaptic levels of DA in the nucleus accumbens, failed to produce an effect on responding for conditioned reward (Kelley and Delfs, 1991*a*). The authors concluded that enhanced levels of accumbens DA are not a sufficient condition for the enhancement of responding for conditioned reward. This view may be seen as

consistent with the conclusions of Taylor and Robbins (1986) that the enhancement of responding for conditioned reward produced by accumbens DA is weak and that this effect is less influenced by the associative significance of environmental stimuli than is the effect of intra-accumbens amphetamine.

It remains that tonic stimulation of DA receptors in the accumbens did augment responding for conditioned reward in some studies (Cador *et al.*, 1991; Chu and Kelley, 1992; Everitt and Robbins, 1992). These data may be understood as follows. It has been reported that microinjections of SKF 38393 into the nucleus accumbens induce neurotoxicity (Kelley *et al.*, 1990). This finding raises the possibility that the enhanced responding for conditioned reward seen with SKF 38393 (Everitt and Robbins, 1992) was related to this action of the drug. This alternate view is supported by the finding that tonic D_1 stimulation with CY 208-243 (Chu and Kelley, 1992) did not enhance responding for conditioned reward. However, a combination of accumbens CY 208-243 plus quinpirole did (Chu and Kelley, 1992). This finding and the finding that responding for conditioned reward was enhanced when DA was infused directly into the nucleus accumbens (Taylor and Robbins, 1984) or when supersensitive accumbens DA receptors were stimulated with a low dose of apomorphine (Taylor and Robbins, 1986) does not exclude the possibility that another DA terminal area, such as the caudate-putamen, may contain a DA D_1 signal that may be sufficient for reward. The small increase in responding for conditioned reward seen with intra-caudate-putamen injections of amphetamine (Kelley and Delfs, 1991*b*; Taylor and Robbins 1984) supports this view. Nevertheless, 6-hydroxydopamine (6-OHDA) lesions of the caudate-putamen failed to disrupt enhanced responding for conditioned reward produce with intra-accumbens injections of amphetamine except perhaps at the highest amphetamine dose (Taylor and Robbins, 1986). As expected, 6-OHDA lesions of the nucleus accumbens eliminated the amphetamine effect but not the conditioned reward effect itself. This latter observation might suggest that the putative reward signal exists in both the nucleus accumbens and the caudate-putamen and that either signal is sufficient for conditioned reward to occur.

Robbins and Everitt (1982) suggested that the effects of pipradrol on responding for conditioned reward may be due to actions in both the mesoaccumbens and nigrostriatal dopaminergic systems after observing that lesions of either system greatly reduced pipradrol-enhanced responding for conditioned reward. This might suggest that the simultaneous disruption of dopaminergic neurotransmission in both structures is required to impair amphetamine-produced enhancement of responding for conditioned reward and the conditioned reward effect itself – a speculation supported by a study showing that avoidance responding, a behaviour which can be understood in terms of reward processes (Beninger, 1983, 1989, 1991), was disrupted only when simultaneous destruction of DA in the nucleus accumbens and caudate-putamen occurred (Koob *et al.*, 1984). Thus, the data of Everitt and Robbins and co-workers do not require rejection of the hypothesis that there may be a signal at the D_1 receptor that is critical for reward-related learning.

Conclusions

Numerous studies have assessed the effects of dopaminergic agents on the acquisition of responding for conditioned reward. When drugs are given systemically, a consistent picture emerges. Indirect-acting agonists, including amphetamine, pipradrol, methylphenidate and similarly acting drugs, increase responding specifically on one of two levers that produces conditioned reward. Direct-acting agonists, such as apomorphine, indiscriminately increase responding on both levers. One theoretical account of this difference suggests that amphetamine-like compounds enhance a signal in dopaminergic neurons that is produced by the presentation of a rewarding stimulus whereas apomorphine, by directly occupying DA receptors, masks the signal. This paradigm may provide a useful strategy for studying the mechanism of action of some dopaminergic compounds.

It might have been expected that systemic treatment with dopaminergic agonists acting selectively at D_1 or D_2 receptors would have produced effects like those seen with apomorphine. However, results revealed that D_2 agonists produced enhanced responding for conditioned reward like that seen with amphetamine; D_1 agonists produced little increase in responding and led to an impairment of the conditioned reward effect at higher doses. These observations led to the suggestion that the putative masking of the dopaminergic reward signal by apomorphine may take place at the D_1 receptor. They suggested further that DA-mediated reward-related learning may result from stimulation of D_1 receptors.

Results from studies evaluating the effects on responding for conditioned reward of centrally administered dopaminergic agents were not immediately compatible with those from studies with systemic drugs. Thus, although there were some inconsistencies, results generally showed that intra-accumbens injections of amphetamine-like drugs, DA itself or agonists specific for either D_1 or D_2 receptors increased responding for conditioned reward. The findings were reconciled by the suggestion that the putative DA signal associated with reward is distributed, occurring in the nucleus accumbens and the caudate-putamen. From this point of view, locally injected agents that augment dopaminergic neurotransmission in the nucleus accumbens, even if they act directly at the D_1 receptor, do not mask the distributed DA signal. This view was supported by the finding that amphetamine injected into some sites in the caudate-putamen led to a small enhancement of responding for conditioned reward and that 6-OHDA lesions of the caudate-putamen reduced the effects of pipradrol on responding for conditioned reward. Further indirect support was provided by the finding that avoidance responding was impaired by 6-OHDA lesions only when both accumbens and caudate-putamen DA were depleted. Thus, it may be that conditioned rewarding stimuli lead to learning by producing a DA signal in both the mesoaccumbens and nigrostriatal dopaminergic systems. It will be the task of future studies to examine this hypothesis.

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